Exhibit 36

Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies

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Prior work suggests an association between perineal use of cosmetic talc and increased ovarian cancer risk. A meta-analysis was performed to examine this hypothesis by evaluating ovarian cancer risk associated with direct exposure of the female genital tract to talc via dusting of contraceptive diaphragms. Data were pooled from epidemiological studies using a general variance-based meta-analytic method that employs confidence intervals. The outcome of interest was a summary relative risk reflecting the risk of ovarian cancer development associated with the use of cosmetic talc on contraceptive diaphragms. Sensitivity analyses were performed to explain any observed statistical heterogeneity and to explore the influence of specific study characteristics on the summary estimate of effect. Initially, combining homogeneous data from nine case–control studies yielded a non-statistically significant summary relative risk of 1.03 (0.80–1.37), suggesting no association between talc-dusted diaphragms and ovarian cancer development. Sensitivity analyses were performed to evaluate the robustness of this finding. All resultant summary relative risks were not statistically significant. The available epidemiological data do not support a causal association between the use of cosmetic talc-dusted diaphragms and ovarian cancer development. *European Journal of Cancer Prevention* 16:422–429 © 2007 Lippincott Williams & Wilkins.

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Introduction

Ovarian cancer represents a major cause of cancer-related morbidity and mortality in the United States with an estimated 22 000 new cases diagnosed in 2005 (Boger-Meigiddo and Weiss, 2005). It is the seventh most common cancer in women and ranks fourth as a cause of cancer deaths among female individuals from the United States, with some 16 000 succumbing to the disease this year. The lethality of ovarian tumors is in large part due to the fact that clinical symptoms tend to occur late in the natural history of the disease and the lack of screening tests allowing for early diagnosis. In fact, approximately 60% of patients are diagnosed with late-stage disease (stage III and IV) vastly diminishing the chance of long-term survival (approximately 10% at 5 years from diagnosis) (Richardson *et al.*, 1985).

Primary prevention of ovarian cancer remains elusive as a clear etiology for the vast majority of cases is unknown. Nonetheless, prior epidemiological research suggests a number of risk factors, including age (older versus younger), nulliparity, first pregnancy after the age of 35 years, diet high in saturated fats, positive family history of ovarian/breast cancer and race (white versus African American) (Baker and Piver, 1994; Tortolero-Luna and Mitchell, 1995; Daly and Obrams, 1998). Clear geographic differences in incidence exist. The highest rates are found in industrialized countries versus underdeveloped nations (Ioka *et al.*, 2003), implicating environmental factors in ovarian cancer etiology. The one exception is highly industrialized Japan (Ioka *et al.*, 2003) with a low annual incidence of approximately 3/100 000. Interestingly, Japanese woman who migrate to the United States experience an increased occurrence of this disease, further suggesting environmental factors in its cause.

In 1982, Cramer *et al.* (1982) published the first study suggesting a link between use of cosmetic talc and the risk of developing ovarian cancer. Subsequently, a number of additional reports have shown a small but increased risk among women using cosmetic talc products, although this finding is not universal (Chang and Risch, 1997). These statistical associations raise concerns that a cause–effect relationship may exist between talc exposure (particularly perineal use) and ovarian carcinogenesis.

Further fueling concerns about this association is the mistaken, but often repeated, assertion that asbestos and talc are biologically similar; that is, they may exhibit similar disease-causing potential (Wong *et al.*, 1999). While talc and asbestos are both silicates, they bear little resemblance structurally or in their biological properties. Asbestos fibers are well recognized human and animal carcinogens with substantial supporting epidemiological and in-vivo evidence available in the published literature (Huncharek, 1986; Mossman and Gee, 1989). Asbestos is known to induce peritoneal (and pleural) mesotheliomas among occupationally and environmentally exposed cohorts and some evidence exists suggesting that asbestos can also cause ovarian neoplasms in humans (Acheson *et al.*, 1982).

Although in the experimental setting translocation of talc particles to the human ovary can occur with deliberate or inadvertent manipulations of patients in the supine position (Wehner, 1998), it is unknown whether cosmetic use of talc in the perineal area can routinely penetrate the female reproductive tract and reach the ovary against physiological forces working in the opposite direction. The existing epidemiological literature focuses primarily on external perineal exposure. It appears, however, that the talc–ovarian cancer hypothesis could be tested with better precision and validity if the exposure to the suspected carcinogen was directly to the reproductive tract. A common route for such an exposure is via talc dusting of contraceptive diaphragms, a well documented practice in the relevant epidemiological literature. Intuitively, the possible association of ovarian cancer with talc-dusted diaphragms appears to provide a more rational test of this cause–effect hypothesis. Therefore, the present report describes the results of a meta-analysis pooling data from nine epidemiological studies examining the risk of ovarian cancer associated with the use of cosmetic talc on diaphragms.

Methods

The methods employed in the design and execution of this analysis have been previously described (Greenland, 1986; Cooper and Hedges, 1994). A study protocol was prospectively developed outlining the purpose and methods; that is, a meta-analysis examining the risk of developing ovarian cancer associated with use of talc-dusted contraceptive diaphragms. Eligibility criteria for study inclusion were determined prospectively as were the specific data elements to be extracted from each published report. The study protocol included details of the planned statistical analysis.

We used a data extraction form designed for recording relevant information from each selected report. Two researchers performed data extraction with differences in extraction forms resolved by consensus. Other data collected but not included in the eligibility criteria were the number of patients in each study, study odds ratios or relative risks, 95% confidence intervals and type of statistical adjustments made, if any, by individual study authors.

Literature search

Information retrieval was performed by previously described methods (Cooper and Hedges, 1994). We conducted a MEDLARS search of the literature published between January 1966 and March 2005, as well as a review of Cancer Lit and the CD-ROM version of Current Contents. The search criteria included all languages. The search terms used were talc exposure and ovarian neoplasms. If a series of articles was published, all data were retrieved from the most recent article. The literature search also included hand searches of bibliographies of published reports, review articles and textbooks.

The initial citations (in the form of abstracts) from this literature search were screened by a physician investigator to exclude those that did not meet inclusion criteria. Reasons for rejection included study designs other than case–control, cohort or randomized controlled trials; animal or in-vivo studies; abstracts; review articles and non-peer reviewed articles. Eligibility criteria included, observational studies or clinical trials enrolling patients with histologically proven ovarian tumors of all histologies, studies enrolling only adult patients (i.e. 18 years or older), availability of data documenting type of talc exposure, in this instance, dusting of diaphragms, and availability of odds ratios or relative risks with 95% confidence intervals for each report or availability of raw data to calculate these parameters.

Statistical analysis

We performed data analysis according to meta-analytic procedures described by Greenland (1986). This method of meta-analysis is a general variance-based method employing confidence intervals. As the variance estimates are based on the adjusted measures of effect, the confidence interval methods do not ignore confounding and are the preferred methodology for pooling observational studies.

For each included study, we derived odds ratios reflecting the risk of developing ovarian cancer associated with the practice of dusting contraceptive diaphragms with cosmetic talc and determined the natural logarithm of the estimated relative risk for each data set followed by calculation of an estimate of the variance. We used the estimate of the 95% confidence interval from each study to calculate the variance of each study's measure of effect.

We calculated a weight for each included analysis as 1/variance followed by a summation of the weights. We then determined the product of the study weight and the natural logarithm of the estimated relative risk and performed a summation of these products. Finally, a summary relative risk and 95% confidence interval were determined.

Before the estimation of a summary relative risk, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the included studies (Greenland, 1986). If Q exceeds the upper tail critical value of χ^2 ($P < 0.10$) at $k-1$ d.f. (where k equals the number of studies analyzed or the number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies do not measure an effect of the same size. In this instance, calculation of a pooled estimate of effect (i.e. relative risks) may be of questionable validity. Possible explanations for the observed heterogeneity must be sought to provide the most rational interpretation of the summary relative risk. Sensitivity analyses and or further stratified analyses are then performed based on the magnitude of Q.

Results

The literature search yielded 17 studies that appeared to meet protocol specifications and full papers were obtained for review (Hartge *et al.*, 1983; Richardson *et al.*, 1985; Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow and Weiss, 1989; Chen *et al.*, 1992; Harlow *et al.*, 1992; Rosenblatt *et al.*, 1992; Tzonou *et al.*, 1993; Purdie *et al.*, 1995; Cook *et al.*, 1997; Goddard *et al.*, 1998; Cramer *et al.*, 1999; Gertig *et al.*, 2000; Ness *et al.*, 2000). Upon further review, nine of these met the specified inclusion criteria. Table 1 provides an overview of the nine reports included in the meta-analysis (Hartge *et al.*, 1983; Richardson *et al.*, 1985; Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow and Weiss, 1989; Harlow *et al.*, 1992; Rosenblatt *et al.*, 1992; Cook *et al.*, 1997; Ness *et al.*, 2000). A total of 2281 ovarian cancer cases and 3608 controls were enrolled in nine case–control studies. Table 1 also specifies which reports were hospital based versus those that were population based. Only Cook *et al.* (1997) and Harlow and Weiss (1989) used both population-derived cases and controls. All of the other studies listed as 'population based' used hospital-derived cases. The individual study odds ratios listed in Table 1 reflect the odds of exposure in cases versus controls, with an odds ratio greater than one suggesting a positive association, that is, an increased risk of ovarian cancer among women using talc-dusted diaphragms.

Before combining all studies to derive a summary estimate of effect (i.e. a summary relative risk) a statistical test for heterogeneity was performed (Q). This gave a value of Q equal to 10.75. With eight degrees of freedom, the P value associated with a Q of this size is 0.22. This indicates that the studies are homogeneous; that is, the studies are measuring an effect of similar

Table 1 Overview of included studies

Study (year)	Number of cases/controls	Percentage eligible cases included	Adjusted OR	95% CI	Adjustments to OR	Epithelial tumors only	Borderline tumors incl.	Stratification by histology	H/P
Booth *et al.* (1989)	235/451	84	0.75	0.85 2.02	Age, SES	Y	Y	N	H
Cook *et al.* (1997)	313/422	64	0.80	0.40 1.40	Age	Y	N+	Y	P
Cramer *et al.* (1982)	215/215	72	1.56	0.62 3.88	Parity, menstrual status	Y	Y	Y	P
Harlow *et al.* (1992)	235/239	59	1.20	0.60 2.40	Parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	Y	Y	Y	P
Harlow and Weiss, 1989	116/158	68	0.50	0.20 1.30	Age, parity, use of oral contraceptives	N/A	All	N/A	P
Hartge *et al.* (1983)	135/171	69	0.80	0.40 1.40	Age, race, hospital	Y	Unknown	N	H
Ness *et al.* (2000)	767/1367	61	0.60	0.30 1.20	Age, gravity, race family HX ovarian cancer, oral contraceptive use, tubal ligation, hysterectomy, breast feeding	Y	Y	N	P
Rosenblatt *et al.* (1992)	77/46	55	3.0	0.80 10.8	Obesity, SES, religion, number of live births, OC use	Y	Unknown	N	H
Whittemore *et al.* (1988)	188/539	NG	1.5	0.63 3.58	Parity, use of oral contra ceptives	Y	Unknown	N	H

SES, socio economic status; OR, odds ratio; CI, confidence interval; H/P, hospital based/population based; N+, separate analyses done for borderline versus invasive tumors.

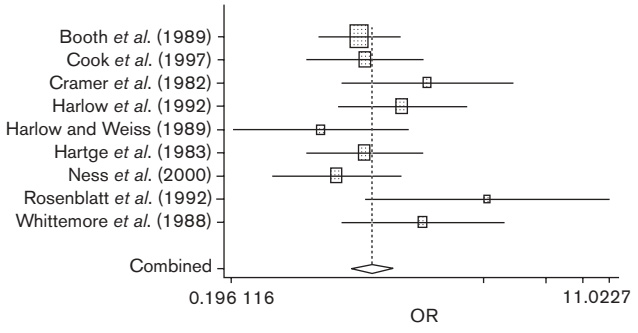
magnitudes. Given the lack of statistical heterogeneity, the data were pooled for calculation of a summary relative risk.

Table 1 shows that adjusted odds ratios ranged from 0.60 (Booth *et al.*, 1989) to 3.0 (Rosenblatt *et al.*, 1992), with adjustment parameters specified along with 95% confidence intervals. Of note, none of the reports showed a statistically significant odds ratio. Initial pooling of data from all nine reports yielded a summary relative risk of 1.03 with a 95% confidence interval of 0.80–1.33, a non-statistically significant result suggesting no association between talc/diaphragm use and ovarian cancer risk (see Fig. 1).

Upon closer scrutiny of the available data, further sensitivity analyses were performed as described below. The data provided by Booth *et al.* (1989) did not explicitly provide data on talc use via contraceptive diaphragms and such use could only be assumed. As the data were questionable in this respect they were dropped from the analysis and a summary relative risk was recalculated. The resultant relative risks was 1.12 with a 95% confidence interval of 0.84–1.48. Therefore, the results remained statistically non-significant despite removal of these data from the summary estimate of effect.

The report by Harlow *et al.* (1992) also represents a potential problem for statistical pooling as the cases in this instance were all patients with 'borderline ovarian tumors'. The exact nature of borderline ovarian tumors in terms of a relationship with their invasive counterparts remains unclear, with some data suggesting differences in epidemiology and etiology (Riman *et al.*, 2001). Whether borderline tumors are precursors of invasive cancers or a separate disease entity is a matter of debate. We therefore recalculated a summary relative risk without inclusion of data from the study by Ness *et al.* (2000). This gave a relative risk of 1.09 with a 95% confidence interval of (0.84–1.41), a non-statistically significant result.

Fig. 1



Forest plot of summary relative risk derived by pooling all available studies using adjusted odds ratios (OR).

All studies except that of Hartge *et al.* (1983) are full research reports with the study by Ness *et al.* (2000) published as a 'Letter to the editor'. Publication in this format is potentially problematic owing to issues related to the 'quality' of the presented data. Letters to the editor normally do not undergo the same type of editorial scrutiny as full research papers. In addition, by their nature, letters are brief notes with limited details presented, precluding rigorous evaluation of methods, results and associated conclusions. In order to address these issues, we dropped the study by Hartge *et al.* from the pooled analysis and, again, recalculated a summary relative risk. This gave a relative risk of 1.07 with a 95% confidence interval of 0.82–1.40. Again, this represents a non-significant finding.

In a prior meta-analysis (Huncharek *et al.*, 2003), we demonstrated a possible bias among studies examining the perineal talc use/ovarian cancer association based on the source of cases. That is, our study suggested that population-based studies may spuriously show a causal association secondary to exposure misclassification to a 'treatment effect' among population-derived cases. Some patients with ovarian cancer will undergo treatment with radiation, chemotherapy and/or surgery. Side effects from treatment may prompt talc use among some of these individuals. Patients may not always make the distinction between pre-diagnosis and post-treatment use. Exposure misclassification among 'prevalent' cases may cause a spurious finding of an association when none, in fact, exists. We therefore recalculated the summary relative risk excluding the studies by Cook *et al.* (1997) and Harlow and Weiss (1989) as these were the only two reports that utilized population-derived cases and controls. The resultant relative risk was 1.15 with a non-statistically significant odds ratio of 0.87–1.53.

Furthermore, this suggests no association between talc use and increased ovarian cancer risk. In fact, if data from the studies by Cook *et al.* (1997) and Harlow and Weiss (1989) are statistically pooled, the summary relative risk is 0.67 with a non-significant confidence interval (i.e. 0.34–1.35). The fact that the population-based relative risk is in the opposite direction (i.e. favoring a protective effect for talc) to that shown in the other case–control studies, further supports the existence of bias in these analyses.

Another methodological consideration is the fact that the definitions of the control groups used across all nine studies are not completely comparable. Some reports defined controls as 'never having used talc' (e.g. Ness *et al.*, 2000), while others used controls defined as not

having used talc on diaphragms (e.g. Cook *et al.*, 1997). We therefore calculated crude odds ratios and 95% confidence intervals using data supplied in the available studies and recalculated a summary relative risk to ensure that the analysis using adjusted odds ratio was not spurious (Table 2). The resultant relative risk was 0.86 (0.59–1.40) (see Fig. 2), a non-statistically significant result suggesting no association between talc use on diaphragms and increased ovarian cancer risk (see Fig. 2). Of note, the test for heterogeneity for this latter analysis gave a value for Q of 7.20 with a P value of 0.52.

Discussion

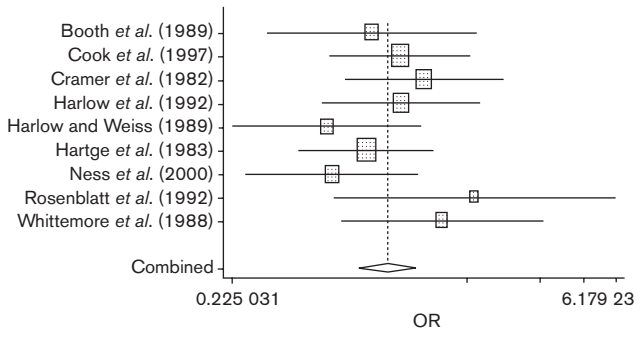
Talc is an important industrial mineral for a number of reasons including its resistance to heat, electricity and acids and its relatively low price. It is used in many commercial applications because of its lamellar platy nature, softness, whiteness, chemical inertness, high melting point and hydrophobic features, among others. For instance, talc is used in the plastic industry owing to its inertness, superior electrical and thermal resistance and its ability to improve the quality of plastic surfaces. It also finds application in the paint industry to increase the smoothness of paint products and in paper manufacturing to reduce the usage of expensive whitening agents because of its high brightness.

Table 2 Crude odds ratios and 95% confidence intervals for included studies

Study (year)	Crude OR	95% CI	Variance	Weight
Booth *et al.* (1989)	0.75	0.33 2.02	0.175	5.70
Cook *et al.* (1997)	0.96	0.52 1.76	0.097	10.2
Cramer *et al.* (1982)	1.18	0.59 2.35	0.125	7.99
Harlow *et al.* (1992)	0.97	0.49 1.92	0.121	8.24
Harlow and Weiss, 1989	0.51	0.22 1.13	0.184	5.43
Hartge *et al.* (1983)	0.72	0.40 1.30	0.090	11.1
Ness *et al.* (2000)	0.53	0.25 1.13	0.147	6.80
Rosenblatt *et al.* (1992)	1.82	0.55 6.34	0.373	2.68
Whittemore *et al.* (1988)	1.38	0.57 3.28	0.204	4.91

OR, odds ratio; CI, confidence interval.

Fig. 2



Forest plot of summary relative risk derived by pooling all available studies using crude odds ratios (OR).

Mineral talc is a magnesium silicate hydroxide belonging to the mineral class, silicate and subclass phyllosilicate. It belongs to the clay mineral group, an important subgroup within the phyllosilicates that contain large percentages of water trapped between the silicate sheets. Clay minerals are divided into four major groups: the kaolinite group, the montmorillonite/smectite group, the illite group and the chlorite group. Talc is a member of the montmorillon/smectite group along with pyrophyllite, vermiculite, sauconite, saponite and nontronite.

Talc also forms pseudomorphs, that is false shapes, of other minerals, replacing them on an atom by atom basis. For instance, talc forms pseudomorphs of quartz, pyroxene, olivine and amphiboles. In nature, it can also be found in association with a number of other minerals, such as serpentine, quartz, olivine and biotite.

In 1982, Cramer *et al.* (1982) published a case–control study suggesting an association between cosmetic talc use on the perineum and increased ovarian cancer risk. Women dusting the perineum with talc or dusting sanitary napkins showed a near doubling of ovarian cancer risk. Unfortunately, in addition to a number of methodological limitations plaguing this report (e.g. only 45% of eligible controls participating), it is important to point out the flawed premise on which it is based. Cramer *et al.* (1982) cite the 'chemical relationship between talc and asbestos' as a major reason for assuming that talc may also be a human carcinogen and that '…the mineral talc is a specific hydrous magnesium silicate chemically related to several asbestos group minerals and occurring in nature with them'.

The above-cited justification for the Cramer *et al.* (1982) study and subsequent work examining a possible cosmetic talc/ovarian cancer link is misguided for a number of reasons. Despite the fact that talc and various forms of asbestos are silicates, they are structurally distinct and belong to different mineral groups and subgroups. That is, amphibole minerals (e.g. tremolite) are inosilicates while talc is a member of the silicate subclass phyllosilicate and the group, clay or montmorillonite/smectite. While serpentines, including serpentine asbestos, are also phyllosilicates, serpentine minerals belong to the kalolinite–serpentine group. The asbestos varieties of serpentine are structurally different from other members of the serpentines in that their brucite layers and silicate layers bend into tubes that produce fibers. Non-fibrous serpentine does not have carcinogenic properties and it is clear that the physical structure of serpentine asbestos is responsible for its disease-causing

potential, not its atomic constituents. It simply does not follow, therefore, that one should assume that talc is carcinogenic simply because it is a silicate and a member of the phyllosilicate subgroup. Structure dictates toxicity/carcinogenicity, not chemical composition.

It is true that in nature, mineral talc can be found in association with both serpentine and amphibole minerals, including the asbestos varieties. It is crucial to understand that the carcinogenic potential of asbestos is well known and abundantly documented in the medical and epidemiological literature (Huncharek, 1986; Mossman and Gee, 1989). Cramer *et al.*'s argument suggesting that pure talc is carcinogenic is based solely on 'guilt by association' rather than on scientific fact. If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogenic effect as it contains a known carcinogen. To then suggest that talc is also carcinogenic simply owing to the fact that it is sometimes found in association with various asbestos minerals in nature is not logical. This reasoning ignores a large body of data regarding the mineralogy of silicates and fails to acknowledge the lack of supporting biological or in-vitro data documenting any carcinogenic potential of pure talc (i.e. uncontaminated by asbestos). A commercial product containing asbestos-contaminated talc could certainly pose a health risk and although prior to the mid-1970s some consumer talc products did, in fact, contain such contamination, the carcinogenic entity is asbestos, not talc (Rohl *et al.*, 1976). It is important to note that since that time, talc product manufacturers voluntarily ensured that such products are asbestos free. Despite this fact, even some recent studies looking at the perineal talc dusting/ovarian cancer risk connection show a weak association (e.g. Mills *et al.*, 2004), further suggesting a spurious finding.

Other evidence that indicates that talc and asbestos have dissimilar biological properties is the fact that talc has been used for decades as a sclerosing agent for both benign and malignant pleural effusions (Viskum *et al.*, 1989). Long-term follow-up studies of these patients have not shown even a single case of lung cancer or mesothelioma resulting from introduction of talc to the pleural cavity (Viskum *et al.*, 1989; Shaw and Agarwal, 2004). Epidemiological studies of talc miners and millers also fail to demonstrate an increased cancer risk (Rubino *et al.*, 1976; Gamble, 1993). In-vivo implantation and injection using asbestos of various types, in contrast, unequivocally induce tumors in experimental animals (Huncharek, 1986).

Despite the above-noted problems, the idea that cosmetic talc poses a possible ovarian cancer risk persists. As reviewed in the present paper and elsewhere (Richardson *et al.*, 1985; Tortolero-Luna and Mitchell, 1995) numerous investigators have examined this possible relationship in a variety of case–control studies and at least one cohort study (e.g. Gertig *et al.*, 2000). Most of these categorized talc use as 'ever versus never' used while others further stratified by particular types of use, for example, perineal dusting, sanitary napkin dusting, condoms, etc. Results differ across studies, with some showing no association (Rosenblatt *et al.*, 1992) while others suggests a 'weak effect' (Purdie *et al.*, 1995), that is odds ratios below 1.5.

In addition to the obvious problems with the premise put forth by Cramer *et al.* (1982) and others, validity of the weak effect shown in a number of other epidemiological studies also remains questionable. The major weaknesses of the existing database include (Boger-Meigiddo and Weiss, 2005) the relatively small sample size of most reports, which limits the statistical power to detect an effect (Richardson *et al.*, 1985), the lack of consistent positive association across studies (Baker and Piver, 1994), the absence of a demonstrable dose–response relationship (Daly and Obrams, 1998), the lack of supporting evidence of talc carcinogenicity from animal or in-vitro analyses (Tortolero-Luna and Mitchell, 1995) and the possible presence of uncontrolled confounding producing a spurious positive association. In fact, some of the available observational studies show an inverse dose–response (Ness *et al.*, 2000) that weighs against a causal association. In addition, no plausible biological mechanism capable of explaining how talc could induce ovarian malignancies exists.

In a study, Heller *et al.* (1996) examined talc particle counts in ovarian specimens from 24 women undergoing incidental oophorectomy and compared these counts with reported frequency and duration of talc use. The study sought to examine the hypothesis of a dose-related risk of epithelial ovarian cancer with perineal talc exposure. Women were considered 'exposed' if they reported talc application to undergarments or directly to the perineum. Talc was detected in all ovaries by either polarized light or electron microscopy. No relationship was found between cosmetic talc burden in healthy ovarian tissue and lifelong perineal talc dusting determined by either microscopic methods. This study raises further questions regarding whether reported associations between perineal talc exposure and ovarian tumors in observational studies reflects a carcinogenic action of talc. The validity of these epidemiologic associations has also been questioned because it is unknown whether talc dust in the perineal area can actually penetrate the female reproductive tract and then translocate to the ovaries against physiological forces working in the opposite direction. The work of Heller *et al.* clearly brings this into question.

Although the epidemiological literature focuses primarily on external perineal exposure to talc, a more valid

assessment of the 'talc hypothesis' would appear to be provided by examining the ovarian cancer risk associated with talc dusting of diaphragms. This particular use of talc results in direct female reproductive tract exposure. Although data on the use of talc-dusted diaphragms have been reported in some epidemiological studies, this literature fails to garner the attention devoted to perineal dusting and no systematic evaluation of this particular literature is available. This probably reflects the fact that perineal dusting is a more common practice than dusting contraceptive diaphragms. Nonetheless, exposure via this latter route is, intuitively, a better 'model' for testing whether talc represents a risk factor for ovarian cancer as the exposure is directly to the female genital tract. Consequently, we performed the above-detailed meta-analysis pooling all available published data on this topic.

Using accepted meta-analytic techniques our analysis was unable to demonstrate any increased risk of ovarian cancer associated with use of talc-dusted diaphragms. Despite performing a number of sensitivity analyses to test the robustness of our findings, the pooled data from over 5000 cases and controls failed to show a positive association. In some studies, the odds ratio was calculated based on an inappropriate control group; for example, individuals who reported no exposure to any talc. For these studies, the crude odds ratio was recalculated based on women who never used talc-dusted diaphragms as the reference group. This summary relative risk was also statistically non-significant.

In summary, our present report, along with our prior meta-analysis pooling data from studies examining the possible ovarian cancer risk associated with perineal talc dusting (Huncharek *et al.*, 2003), does not provide evidence of a causal relationship. In the context of 'weak associations', many sources of bias and uncontrolled confounding can contribute to the finding of a spurious association. Recall bias in case–control studies, lack of a demonstrated dose–response in many published analyses, lack of a coherent biological mechanism for possible talc carcinogenicity and lack of supporting animal or in-vitro data demonstrating the carcinogenic potential of talc all argue against a causal relationship. These limitations and inconsistencies have also been discussed in detail elsewhere (Wehner, 1994; Muscat and Barish, 1998). As ovarian cancer remains a major cause of cancer-related morbidity and mortality in the United States, further work is needed to clearly define modifiable risk factors in an attempt to improve disease prevention.

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Exhibit 37

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 29:435–439 (1996)

Asbestos Exposure and Ovarian Fiber Burden

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Epidemiologic studies suggest increased risk of epithelial ovarian cancer in female asbestos workers and increased risk of malignancy in general in household contacts of asbestos workers. Ovaries were studied from 13 women with household contact with men with documented asbestos exposure and from 17 women undergoing incidental oophorectomy. Ovarian tissue was examined by analytic electron microscopy.

Significant asbestos fiber burdens were detected in 9 out of 13 women with household asbestos exposure (69.2%), and in 6 out of 17 women who gave no exposure history (35%). Three exposed women had asbestos counts over 1 million fibers per gram wet weight (23%), but only 1/17 women without an exposure history had a count that high (6%). Although asbestos has been documented as a contaminant of some older cosmetic talc preparations, the chrysotile and crocidolite types of asbestos we detected are more indicative of background and/or occupational exposure.

This study demonstrates that asbestos can reach the ovary. Although the number of subjects is small, asbestos appears to be present in ovarian tissue more frequently and in higher amounts in women with a documentable exposure history. © *1996 Wiley-Liss, Inc.*

KEY WORDS: asbestos, ovary, talc, environmental exposure

INTRODUCTION

Epidemiologic evidence suggests that there is an increased risk of ovarian carcinoma in female asbestos workers [Acheson et al., 1982; Graham and Graham, 1967; Keal, 1960; Newhouse et al., 1972, 1985; Wignall and Fox, 1982], and animal data show changes resembling early ovarian carcinoma after intraperitoneal injection of asbestos [Graham and Graham, 1967]. In addition, household contacts of asbestos workers have been shown to be at increased risk of developing asbestos-related disease [Joubert et al., 1991; Roggli and Longo, 1991], so female household contacts of asbestos workers may also be at risk of ovarian exposure to asbestos. There is literature that supports that perineal talc exposure increases the risk of ovarian carcinoma. However, some of these data have been clouded by the fact that cosmetic talc was often contaminated with asbestos in the past, particularly before 1976 [Cramer et al., 1982]. Particulate matter can reach the female peritoneal cavity via the transvaginal route [Egli and Newton, 1961; Henderson et al., 1986; Joubert et al., 1991]. A woman exposed to her husband's occupationally contaminated laundry may have asbestos enter the peritoneal cavity by passive transfer, or even by sexual relations. The purpose of this study was to determine whether women exposed to asbestos have a high asbestos fiber burden in their ovaries.

MATERIALS AND METHODS

Eligible women were contacted by postcard with the assistance of a law firm specializing in asbestos-related claims. Women with household contact to asbestos, as documented by interview, and who had themselves previously undergone ovarian surgery, were invited to participate. No women with direct occupational exposure responded.

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TABLE I. Demographics and Pathologic Findings Among 8 Patients With Household Contacts Evaluated for Asbestos-Related Disease Oophorectomized Between 1973–1994, and 5 Oophorectomized Patients With a History of Asbestos Exposure From the Columbia Presbyterian Medical Center Benign Neoplasm Study, 1992–1993

Subject	Reason for surgery	Asbestos-fibers per gram wet weight	Limits of detection	Asbestos exposure
1	Papillary serous cystadenocarcinoma of ovary	490,813 chrysotile: crocidolite 1:2	40,901	Husband—pipefitter with asbestos
2	Mucinous cystadeno-carcinoma of ovary	below detectible limits	26,267	Father—died of mesothelioma; husband—asbestosis (both insulators)
3	Endometrial adenocarcinoma	1,227,031 chrysotile: crocidolite 1:1	15,338	Husband—asbestosis, carpenter in a factory
4	Atypical hyperplasia of endometrium	74,167 chrysotile	18,542	Husband—insulator, died of lung cancer
5	Endometriosis of ovary	328,913 chrysotile	41,114	Father and aunt—worked in asbestos plant; father—died of lung cancer, aunt of asbestosis
6	Leiomyoma uteri	3,438,636 chrysotile	42,983	Father—asbestosis, asbestos and insulation worker
7	Serous cystadenoma of ovary, fibroma of ovary	below detectible limits	42,983	Husband—insulation worker
8	Endometrial adenocarcinoma	1,513,00 chrysotile: tremolite 4:1	37,825	Husband—died of asbestosis;[a] worked as carpenter and with concrete
9[a]	Cystadenofibroma of ovary	49,081 chrysotile: crocidolite 1:1	24,541	2 brothers—construction workers
10[a]	Benign epithelial cyst of ovary	below detectible limits	37,825	Father—shipyard worker and school engineer
11[a]	Serous cystadenoma of ovary	298,618 chrysotile	24,885	Household member—shipyard worker × 4 years
12[a]	Cystadenofibroma of ovary	788,020 crocidolite	157,604	Father—shipyard worker
13[a]	Cystadenofibroma of ovary	below detectible limits	42,983	Household contact —construction/insulation × 3 years

[a]Subjects from Columbia Presbyterian Medical Center Benign Neoplasm Study.

Women with both benign and malignant disease responded. Women undergoing oophorectomy for benign ovarian neoplasms at Columbia Presbyterian Medical Center who were interviewed in depth for another study were available as controls and were included after ascertaining asbestos exposure history and availability of nonneoplastic ovarian tissue for analysis. These women were chosen for the availability of interviews as well as tissue. Five of these women were found to have sustained asbestos exposure. There were 13 exposed subjects and 17 women who gave no history of exposure. Tissue from two stillborn ovaries was also analyzed. Tissue blocks of benign adjacent or contralateral ovarian tissue as available were obtained, and analytic electron microscopy was performed according to the subsequent protocol. Hematoxylin and eosin stained sections of analyzed tissue were examined. There was no evidence of response to asbestos such as foreign body giant cell reactions or fibrosis in the tissue. Ovarian tissue does not undergo fibrosis as does lung.

Analytic Electron Microscopy Protocol

Ovarian tissue in blocks was deparaffinized, rehydrated, blotted dry, and weighed. Digestion with 5% KOH was performed at 70°C for 2–4 hr. After complete digestion, the tissue was centrifuged at 12,000 rpm for 20 min. The KOH was removed, leaving a pellet to which approximately 20 ml of distilled water was added. The pellet was resuspended by using a microultrasonic cell disrupter at 50 watts for 5 sec. Centrifugation, distilled water wash, and

TABLE II. Demographics and Pathologic Findings Among 17 Oophorectomized Patients With No History of Asbestos Exposure—Columbia Presbyterian Medical Center Benign Neoplasm Study, 1992–1993

Control	Reason for surgery	Asbestos fibers per gram wet weight	Limits of detection	Exposure history
11 subjects	4 serous cystadenomas/simple cyst 3 benign cystic teratoma/struma ovarii 2 endometrioma/endometriosis 1 fibrothecoma 1 mucinous cystadenoma	Below detectable limits	None greater than 27,267	None
1	Endometriosis, benign cystic teratoma	525,871 chrysotile: crocidolite 1:2	17,529	None
2	Endometrioma of ovary	109,069 chrysotile: crocidolite 1:1	6,817	None
3	Benign cystic teratoma of ovary	33,849 chrysotile	8,462	None
4	Endometrioma of ovary	147,244 chrysotile: crocidolite 1:2	12,270	None
5	Serous cystadenoma of ovary	98,163 crocidolite	12,270	None
6	Benign cystic teratoma of ovary	2,181,388 chrysotile	27,267	None

microultrasonic cell disrupter were repeated 3 times. The distilled water was removed and the pellet was resuspended in 5–10 ml of distilled water. Ten-µl drops of the final suspension were placed on nickel Formvar and carbon-coated locator grids and air dried. Transmission electron microscopy to identify fibers, and their size was performed. The identity of the fibers was determined by energy-dispersive spectroscopy and confirmed by electron diffraction (SAED). Grids were viewed at both 10,000 and 19,000 diameters. All fibers observed were counted.

Routinely, as they are opened or distilled water at each filtering, all solutions are checked for detectable limits of asbestos fibers. All places where asbestos could have contaminated the specimen, such as paraffin, are also controlled for paraffin blocks from each different source. All solutions are checked by passing the fluids through a 0.1-µm Nucleopore filter to maximize the efficiency of detecting and counting fibers present in these solutions and materials. The solutions that are routinely tested are distilled water, KOH, and xylene. If detectable levels of asbestos fibers exist in the solutions used to initially fix and process the tissue because they came from different hospitals, at which it was not possible to test these solutions directly, they would be detected in the paraffin controls. We have yet to identify detectable levels in any of the solutions or paraffin.

RESULTS

A summary of the results can be seen in Tables I and II. Nine of the 13 women exposed to asbestos had asbestos in their ovarian tissue (69.23%), with 3 (23%) of them having counts over 1 million fibers per gram of wet weight. Among the controls, 6/17 women had detectable asbestos in their ovaries (35%), with only 1 (6%) patient with a count over 1 million fibers per gram wet weight. In addition, talc was detected in 11/13 exposed women (85%) and in all 17 controls (100%). No asbestos or talc was detected in the stillborn material.

All fibers were counted and analyzed for type and size. The results of that analysis are summarized in Table III. In general, the fibers were relatively small with regard to length and narrow in diameter. However, the great majority of fibers were greater than 3 µm with a minimum aspect ratio of 10. Except for one case, in which tremolite was observed, the fibers were either chrysotile or crocidolite, or both.

DISCUSSION

Epithelial ovarian carcinoma is a major cause of female mortality [Greene et al., 1984]. Epithelial ovarian cancer

TABLE III. Asbestos Fibers in Ovarian Tissues: Type, Number, and Dimensions

Subject	No. of fibers	Fiber type	<3 μm long	3–10 μm long	>10 μm long	<0.1-μm diameter	0.1–0.2-μm diameter	>0.2-μm diameter
1[a]	4	Chrysotile	1	2	1	4	—	—
	8	Crocidolite	1	7	—	4	4	—
3[a]	40	Chrysotile	2	28	10	35	5	—
	40	Crocidolite	3	31	6	30	10	—
4[a]	4	Chrysotile	—	3	1	4	—	—
5[a]	8	Chrysotile	1	6	1	7	1	—
6[a]	80	Chrysotile	5	62	13	71	9	—
8[a]	32	Chrysotile	2	22	8	22	10	—
	8	Tremolite	1	7	—	—	6	2
9[a]	1	Chrysotile	—	1	—	1	—	—
	1	Crocidolite	—	1	—	1	—	—
11[a]	12	Chrysotile	1	9	2	8	4	—
12[a]	20	Crocidolite	2	14	4	12	8	—
1[b]	10	Chrysotile	1	8	1	4	6	—
	20	Crocidolite	2	18	—	17	3	—
2[b]	8	Chrysotile	—	7	1	5	3	—
	8	Crocidolite	1	7	—	6	2	—
3[b]	4	Chrysotile	—	4	—	3	1	—
4[b]	4	Chrysotile	—	4	—	3	1	—
	8	Crocidolite	1	7	—	7	1	—
5[b]	8	Crocidolite	—	8	—	6	2	—
6[b]	80	Chrysotile	7	58	15	68	12	—

[a]From Table I.
[b]From Table II.

develops from the surface epithelium of the ovary, which is embryologically derived from the same tissue as the mesothelium of the abdominal cavity, the celomic epithelium [Falkson, 1985]. Thus, ovarian carcinoma and malignant mesothelioma of the peritoneal cavity are believed by some to be related neoplasms [Parmely and Woodruff, 1974]. Asbestos causes malignant mesothelioma, and there is evidence to support it as an etiology in ovarian carcinoma as well [Acheson et al., 1982; Falkson, 1985; Graham and Graham, 1967; Keal, 1960; Newhouse, 1979; Newhouse et al., 1972, 1985; Whittemore et al., 1988; Wignall and Fox, 1982].

Intraperitoneal injection of tremolite asbestos into guinea pigs and rabbits was shown to cause epithelial changes in their ovaries similar to those seen in early ovarian cancer [Graham and Graham, 1967]. These investigators also found birefringent crystalline material near these epithelial changes, but no further attempt was made to identify the material. No such material was found in controls. Asbestos fibers have been shown to be cytotoxic to Chinese hamster ovary (CHO) cells, an epithelioid cell culture line [Neugut et al., 1978].

Several investigators have cited an increased mortality from ovarian cancer in female asbestos workers exposed as gas mask assemblers or other factory workers [Acheson et al., 1982; Newhouse, 1979; Newhouse et al., 1972, 1985; Wignall and Fox, 1982]. In addition, it is known that household contacts of asbestos exposed workers are also at increased risk of developing malignant disease in general [Joubert et al., 1991; Roggli and Longo, 1991]. In a study of 52 histologically confirmed malignant mesotheliomas in women, most with no occupational exposure of their own, a significant number were found to have husbands or fathers who worked in an asbestos-related industry [Vianna and Polan, 1978], and the findings suggested indirect exposure to a husband as the most important factor.

The fact that exposure to a husband is more significant than exposure to a father suggests a possible role for sexual contact as a transporting vector for asbestos fibers. Household exposure has been related to the asbestos dust on the workers' clothing, with risk to those who launder the clothing [Joubert et al., 1991]. While this may be the exposure source in wives as well as in daughters, it is possible that sexual contact with a male contaminated with asbestos fibers introduces those fibers into the vagina of his partner, where they can reach the peritoneal cavity. There is evi-

dence of transport of particulate matter into the female peritoneum by the transvaginal route, in both human and animal studies [Egli and Newton, 1961; Henderson et al., 1986; Venter and Iturralde, 1979]. Whittemore et al. [1988] suggested that vaginal exposure to particulate matter such as asbestos and talc was a potential risk factor for intraperitoneal ovarian exposure. Her conclusion was based on finding that in talc-exposed women, a previous history of hysterectomy or tubal ligation, which blocks peritoneal access, was protective against ovarian cancer.

Talc has also been implicated as a possible etiologic agent in ovarian cancer [Harlow et al., 1989, 1992], and this is related to the asbestos problem in several ways. Aside from the chemical similarities between the two, many cosmetic talcs contained significant amounts of asbestos, particularly prior to 1976 [Cramer et al., 1982]. The significance of the detection of talc in the majority of the exposed women and in all women giving no exposure history is unclear, and further studies are under way to further elucidate this association.

CONCLUSIONS

In our study, the women with a positive exposure history had asbestos detected in their ovaries more frequently, and in higher counts. None of the exposed subjects in this study was directly occupationally exposed, but all were passively exposed to a household contact. It is unclear why so many of the women giving no exposure history did have detectable asbestos in their ovaries, although it is known that there is a background level of asbestos in the lung tissue of nonexposed individuals. All our available control patients were selected from a group of extensively interviewed women with benign ovarian neoplasms. Further studies are aimed at women with no ovarian pathology. The significance of the finding of asbestos in ovaries requires further investigation.

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Exhibit 38

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TRANSPORT OF PARTICULATE MATTER THROUGH THE HUMAN FEMALE GENITAL TRACT

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Summary. A small quantity of India ink placed in the uterine cavity before laparotomy was found to have been transferred to the Fallopian tubes in more than 50% of the observed patients. Transfer from the cervical canal occurred in nearly 30% of patients but transfer from the vagina occurred only once in thirty-seven observations. The influence of the phase of the menstrual cycle, the use of Syntocinon and the state of the Fallopian tubes is considered.

Rowson (1955) showed that radio-opaque material introduced into the cervix of the cow at artificial insemination was spread rapidly throughout the whole of the uterine horn; at oestrus, the spread extended into the Fallopian tube but, during the luteal phase, it was limited to the horn. The rate of transport of spermatozoa in the cow has been shown to be influenced by oxytocin. (Van-Demark & Moeller, 1951). In the human subject, Egli & Newton (1961) found that carbon particles passed from the vagina to the Fallopian tubes within a few minutes of placement in two out of three patients.

A quantity of India ink (a collodial suspension of carbon) was placed at a selected level in the genital tract of a number of patients about to undergo an abdominal surgical procedure. Some received an intramuscular injection of 2 units Syntocinon at the same time. At operation 15 min to 24 hr later, the Fallopian tubes were examined macroscopically and the presence or absence of black material was recorded. A total of 178 operations was performed, 135 of these were for abdominal tubal ligation, twenty-eight for hysterectomy—in one, oophorectomy was performed—and fourteen were for tubal diathermy under a laparoscopic technique. The results of the study are shown in Table 1.

In the majority of the positive cases, there was no doubt that the carbon particles were present in the Fallopian tubes. In some, there had been spill into the peritoneal cavity in quantities sufficient to require swabbing out. In the tube itself, the carbon suspension frequently seemed to be held in short segments, giving the tube a beaded appearance.

Injection of the India ink into the uterus rarely caused difficulty and was made without any force. Injection into the cervical canal was often difficult, with immediate flow back into the vagina and it is possible that some of the injected material reached the uterine cavity directly. The findings after cervical injection must accordingly be suspect.

From the uterine cavity, transport of the India ink to the Fallopian tubes was

slightly more frequent in the secretory phase (64%) than in the proliferative phase (54%). From the cervix, this finding was reversed; 22% in the secretory phase, and 33% in the proliferative phase.

Syntocinon had little effect on the outcome. Considering both levels of the uterus together, there were 48% of positives in the Syntocinon-treated group and 47% in the untreated group.

TABLE 1

TRANSPORT OF INDIA INK TO THE FALLOPIAN TUBES FOLLOWING DEPOSITION INTO THE GENITAL TRACT

Treatment		*All cases*	*With Syntocinon*	*Without Syntocinon*	*Within 30 min of injection*	*Within 60 min of injection*
I. Injection of 0·2 ml ink into uterine cavity						
A. Proliferative phase of cycle	Positive	27 (54%)	7	20	2	6
	Negative	23	5	18	3	5
B. Secretory phase of cycle	Positive	23 (64%)	3	20	3	7
	Negative	12	4	8	2	2
II. Injection of 0·2 ml ink into cervical canal						
A. Proliferative phase of cycle	Positive	11 (33%)	3	8	—	—
	Negative	22	4	18	—	—
B. Secretory phase of cycle	Positive	4 (22%)	1	3	—	—
	Negative	14	2	12	—	—
C. Post menopause	Positive	1	—	—	—	—
	Negative	3	—	—	—	—
D. Post abortion	Positive	1	—	—	—	—
	Negative	0	—	—	—	—
III. Deposition of 2 ml ink into vagina (12 to 24 hr before operation)						
A. Proliferative phase of cycle	Positive	1	—	1	—	—
	Negative	17	14	3	—	—
B. Secretory phase of cycle	Positive	0*	19	—	—	—
	Negative	0	19	—	—	—

Positive—carbon particles present. Negative—no carbon particles present.

* In one of these cases, where hysterectomy was performed, carbon particles were found in the uterus.

In one patient, subsequent histology revealed gross chronic inflammation of the Fallopian tubes. In this patient, a large amount of the carbon suspension was present in the tube. Fox & Fox (1967) and de Carteret (1967) have suggested that the human female orgasm assists sperm transport by drawing the spermatozoa up into the uterus by suction. This is denied by Masters & Johnson (1966). Since many fertile women fail to experience an orgasm, it is tempting to consider that the motility of the spermatozoon is purposive. There is no evidence of any chemotactic response by spermatozoa other than their particular mobility in the thin mucus of the oestrogenized cervix. Mattner (1963) considers

that the effective direction of travel of motile spermatozoa depends on their relative concentrations at either end of the passage under consideration. This may be regarded as a process of accelerated diffusion, the purpose of the sperm motility being to prevent sedimentation.

In the investigation described, there was no doubt that the inert carbon material was frequently and rapidly transported from the uterus to the tubes in both phases of the menstrual cycle. From the vagina to the uterus, passage of the marker was observed only twice in thirty-seven investigations. This is in contrast to the findings of Egli & Newton (1961), who found two positives out of of three, but the difference may be due to the fact that in the series described here the patients were placed in the Trendelenberg position after the abdomen had been opened. In this position, and especially under anaesthesia, there is a negative intra-abdominal pressure which may be sufficient to draw up material from the vagina into the uterus, particularly through a relaxed cervix. The one positive in this group was a woman who had had six children and had a lacerated cervix.

It is suggested that in man the motility of the spermatozoa is a major factor in overcoming the cervical barrier. Above the level of the cervix, the activity of the upper genital tract, including the Fallopian tubes, ensures the rapid dispersion of any material throughout its whole length. This can occur even when the Fallopian tubes are chronically inflamed.

I would like to express my thanks to Dr R. Rewell, pathologist, for his help and to my Ward Sister, Miss M. Connah, for her patience and co-operation.

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Exhibit 39

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Food and Drug Administration
College Park, MD 20740

APR 1 - 2014

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RE: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP

Dear Dr. Epstein:

This letter is in response to your two Citizen Petitions dated November 17, 1994 and May 13, 2008, requesting that the Food and Drug Administration (FDA or the Agency) require a cancer warning on cosmetic talc products. Your 1994 Petition requests that all cosmetic talc bear labels with a warning such as "Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer." Additionally, your 2008 Petition requests that cosmetic talcum powder products bear labels with a prominent warning such as: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer." Further, both of your Petitions specifically request, pursuant to 21 CFR 10.30(h)(2), a hearing for you to present scientific evidence in support of this petition.

We have carefully considered both of your Petitions. We are committed to the protection of the public health and share your interest in reducing the risk of ovarian cancer. Current regulations state that cosmetic products shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with a product. FDA may publish a proposal to establish a regulation prescribing a warning statement on behalf of a petitioner if the petition is supported by adequate scientific basis on reasonable grounds.

After careful review and consideration of the information submitted in your Petitions, the comments received in response to the Petitions, and review of additional scientific information, this letter is to advise you that FDA is denying your Petitions. FDA did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer.

For this reason and for the additional reasons described below, FDA is denying your Petitions.

I. Discussion

The basis of your request, throughout both Petitions, can be summarized as comprising three major points:

1. Talc may be associated with asbestos.
2. Talc is a carcinogen based on the findings of a 1993 National Toxicology Program study.
3. Epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

As the points you raise in your Petitions concern the chemistry and toxicology of talc, the epidemiology associated with talc use, and the etiology of ovarian cancer, commensurate reviews were conducted to assess your request.

Chemistry Findings:

Asbestos is a known carcinogen and your first major point is that talc may be associated with asbestos. As evidence that talc cosmetic products contain asbestos, you first cite a 1968 survey of 22 talcum products that found fiber content averaging 19% in all 22 products. This author further concludes that "the fibrous material was predominantly talc but probably contained minor amounts of tremolite, anthophyllite, and chrysotile [asbestos-like fibers] as these are often present in fibrous talc mineral deposits …"

You then cite a follow up study from 1971-1975 that examined 21 samples of consumer talcums and powder and concluded that cosmetic grade talc was not used exclusively in these products. This study found the presence of asbestiform anthophyllite and tremolite, chrysotile, and quartz. From these two citations, one may infer that currently available talc-containing cosmetic products are presently contaminated with asbestos, a known carcinogen. Unfortunately, you did not present any original data on the chemical composition of talc currently being used in cosmetics talc products or data linking these findings to currently used talc.

It has been reported in the scientific literature that most talc products in world trade are impure as a result of the geological processes involved in the formation of talc deposits. Further, talc containing asbestos fibers such as tremolite asbestos or chrysotile are sometimes encountered. However, large deposits of high purity, asbestos-free talc do exist and talc purification techniques have been developed which can be used to improve talc quality. Thus, while it has been reported in the past that cosmetic talc has been contaminated with asbestos, it has been also reported that asbestos-free talc deposits do exist. In addition, techniques do exist for the purification of talc in order to improve its quality. You have not provided evidence that asbestos contaminated talc-containing cosmetic products are currently being marketed, since the data submitted is almost 40 years old.

Because safety questions about the possible presence of asbestos in talc are raised periodically, in 2009 FDA conducted an exploratory survey of currently marketed cosmetic-grade raw material talc and finished cosmetic products containing talc. This survey analyzed cosmetic-grade raw material talc from four suppliers out of a possible group of nine suppliers we had requested talc samples from, along with thirty-four talc-containing cosmetic products currently available in the Washington, D.C. metropolitan area for the presence of asbestos. In order to cover as broad a product range as possible, samples identified for testing included low, medium, and high priced products, along with some from "niche" markets. The cosmetic products identified as containing talc included eye shadow, blush, foundation, face powder, and body powder.

The survey found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc. While FDA found this data informative, the results were limited by the fact that only four suppliers submitted samples and by the number of products tested. They do not prove that all talc-containing cosmetic products currently marketed in the United States are free of asbestos contamination. As always, when potential public health concerns are raised, we will continue to monitor for new information and take appropriate actions to protect the public health. You may wish to see more on this survey on our website at http://www.fda.gov/Cosmetics/ProductandIngredientSafety/SelectedCosmeticIngredients/ucm293184.htm.

Toxicology Findings:

Your second major point is that talc is a carcinogen with or without the presence of asbestos-like fibers. The basis to this claim is that in 1993, the National Toxicology Program (NTP) published a study on the toxicity of non-asbestiform talc and found clear evidence of carcinogenic activity.

This NTP report concluded that cosmetic-grade talc caused tumors in animals, even though no asbestos-like fibers were found. The report made the following observations:

- There was some evidence of carcinogenic activity in non-asbestiform talc from inhalation studies in male rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland.
- There was clear evidence of carcinogenic activity of talc in female rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.
- There was no evidence of carcinogenic activity of talc in male or female mice exposed to 6 or 18 mg/cubic meter.

However, this study lacks convincing scientific support because of serious flaws in its design and conduct, including:

- The investigators used micronized talc instead of consumer-grade talc resulting in the experimental protocol not being reflective of human exposure conditions in terms of particle size.

- Investigators conceded that they had problems with the aerosol generation system; whereby, the target aerosol concentrations were either excessive or not maintained during 26 of the 113-122 weeks of the study.
- The study did not include positive and negative dust controls which would have permitted an "exact assessment" of the talc's carcinogenicity relative to the two control dusts.

In light of these shortcomings, a panel of experts at the 1994 ISRTP/FDA workshop declared that the 1993 NTP study has no relevance to human risk.

In addition, we reviewed relevant toxicity literature (consisting of 15 articles from 1980 to 2008), not cited in your Petitions, to determine if there was additional support at this point in time to for your suggested warning label. Scientific literature on studies of acute exposure effects, subchronic exposure effects, chronic exposure or carcinogenicity effects, developmental or reproductive toxicity, and genotoxicity effects were reviewed. As a result of the review of this relevant literature, FDA did not find enough additional support at this point in time for your suggested warning label.

Epidemiology and Etiology Findings:

Your third major point is that epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

After consideration of the scientific literature submitted in support of both Citizen Petitions, FDA found:

1 The exposure to talc is not well-characterized; it is not known if the talc referred to in the scientific studies was free of asbestos contamination; various consumer brands or lots of talc were not identified; and contamination of talc by asbestiform minerals or other structurally similar compounds was not ruled out.

2 Several of the studies acknowledge biases in the study design and no single study has considered all the factors that potentially contribute to ovarian cancer, including selection bias and/or uncontrolled confounding that result in spurious positive associations between talc use and ovarian cancer risk.

3 Results of case-controls studies do not demonstrate a consistent positive association across studies; some studies have found small positive associations between talc and ovarian cancer but the lower confidence limits are often close to 1.0 and dose-response evidence is lacking.

4 A cogent biological mechanism by which talc might lead to ovarian cancer is lacking; exposure to talc does not account for all cases of ovarian cancer; and

5 there was no scientific consensus on the proportion of ovarian cancer cases that may be caused by talc exposure.

6 The conclusion of the International Agency for Research on Cancer that epidemiological studies provide limited evidence for the carcinogenicity of perineal use of talc based body powder and the IARC classification of body-powder talc as group-2B, a possible carcinogen to human beings, is persuasive, but the results of the Nurses' Health Study, a large prospective cohort study, revealed no overall association with ever talc use and epithelial ovarian cancer.

Per the etiology review, approximately 10% of epithelial ovarian cancers are associated with inherited mutations. The remaining 90% of epithelial ovarian cancers are not related to these genetic mutations are non-hereditary. They have been historically classified based on histology as borderline/low malignant potential, serous, endometrioid, mucinous, and clear-cell.

Two theories have historically dominated on the cause of epithelial ovarian cancer and these are the "incessant ovulation hypothesis" and the "gonadotropin hypothesis." In addition to these endogenous factors, the role of exogenous factors via retrograde transport of noxious substances (e.g. carcinogens, particulates such as talc and asbestos, endometriosis and infectious agents) from the vagina and uterus into the Fallopian Tubes and peritoneal cavity have been studied extensively as a possible risk factor for ovarian cancer.

While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable. It is, therefore, plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian Tubes, ovaries and peritoneum may elicit a foreign body type reaction and inflammatory response that, in some exposed women, may progress to epithelial cancers. However, there has been no conclusive evidence to support causality.

The best evidence for an association or causal relationship between genital talc exposure and ovarian cancer comes from epidemiologic data which show a statistically significant but modest increased risk of epithelial ovarian cancer, especially with serous histology, among women with a history of genital dusting with talcum powder. While the growing body of evidence to support a possible association between genital talc exposure and serous ovarian cancer is difficult to dismiss, the evidence is insufficient for FDA to require as definitive a warning as you are seeking.

Request for hearing

In addition to your request for a warning label, you also requested a hearing, under 21 CFR 10.30(h)(2), so that you can present scientific evidence in support of your petitions.

Under this regulation, FDA may deny a citizen petition request for a hearing if the data and information submitted (even if accurate), are insufficient to justify the determination urged. In consideration of your request, we conducted an expanded literature search dating from the filing of the petition in 2008 through January 2014. The results of this search failed to identify any new compelling literature data or new scientific evidence.

Since we find that the data and information are insufficient to justify the determination you request and we did not identify any new compelling literature data or new scientific evidence, FDA is also denying your hearing request.

II. Conclusion

FDA appreciates the goals of the Cancer Prevention Coalition and FDA supports the goal of reducing the rate of ovarian cancer. Although FDA is denying the Cancer Prevention Coalition's petitions for the reasons discussed above, the Agency shares your commitment to the public health.

Sincerely,

Steven M. Musser, Ph.D.
Deputy Director for Scientific Operations
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and Applied Nutrition

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